

## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PXWO00090/2005	<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/EP2005/001659	International filing date (day/month/year) 16.02.2005	Priority date (day/month/year) 17.02.2004	
International Patent Classification (IPC) or national classification and IPC INV. C07D231/06 A61K31/415 A61P3/04 A61P25/30 A61P35/00			
Applicant LABORATORIOS DEL DR. ESTEVE S.A. ET AL			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand  26.09.2005		Date of completion of this report  12.04.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized officer  Hoepfner, W  Telephone No. +49 30 25901-337	



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ON PATENTABILITY**

International application No.  
PCT/EP2005/001659

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-59 as originally filed

**Claims, Numbers**

1-35 as originally filed

**Drawings, Sheets**

1/2, 2/2 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. IV Lack of unity of invention**

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1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
  - ☐ paid additional fees.
  - ☐ paid additional fees under protest.
  - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
  - ☐ the parts relating to claims Nos. .

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-35
	No: Claims	
Inventive step (IS)	Yes: Claims	1-35(part)
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-35
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item IV**

**Lack of unity of invention**

The international patent application WO-A-02080909 discloses derivatives of 1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-carboxamide and their use in the treatment of cancer (see page 1, lines 14, 15, page 4, Formula (I); page 4, line 28, page 6, lines 31-34). These compounds have in common the same structural feature as the compounds of formula (I) of claim 1, namely 1,5-diphenyl-4,5-dihydro-1H-pyrazol having a carbonyl group at position 3.

Hence, the distinguishing feature between the said compounds of formula (I) and the said compounds of D1 has to be seen as the particular kind of substituent  $R^3$  at the carbonyl group, namely

- firstly a cyclic substituent and
- secondly a group  $-NR^4R^5$ .

However, with the presence of 2 different distinguishing features and with the umbrella of any common structural feature being lost, the subject-matter of the present claim 1 can no longer be regarded as being unitary within the meaning of Rule 13 PCT and is therefore split into 2 different inventions (non-unity *a posteriori*), the said inventions being as follows:

- provision of a compound of formula I having a substituent  $R^3$  represented by a cyclic group (invention #1) and
- provision of a compound of formula I having a substituent  $R^3$  represented by a group  $-NR^4R^5$  (invention #2).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

- D1: WO 02/080909 A (LABORATORIOS DEL DR. ESTEVE, S.A; CUBERES-ALTISENT, MARIA ROSA; BERROC) 17 October 2002 (2002-10-17)
- D2: WO 88/06583 A (E.I. DUPONT DE NEMOURS AND COMPANY) 7 September 1988 (1988-09-07)
- D3: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 9 April 1991 (1991-04-09), XP002335745 retrieved from STN accession no. 1991:77052

- D4: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 19 October 2001 (2001-10-19), XP002335857 retrieved from STN Database accession no. 2001:915250
- D5: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 10 January 2003 (2003-01-10), XP002335858 retrieved from STN Database accession no. 1993:2433
- D6: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 April 2001 (2001-04-22), XP002335859 retrieved from STN Database accession no. 1958:40527
- D7: WO 92/03421 A (E.I. DU PONT DE NEMOURS AND COMPANY) 5 March 1992 (1992-03-05)

### Novelty

The document D1 discloses 3-aminocarbonyl derivatives of pyrazoline and their use in the preparation of medicaments for the treatment of cancer (see page 1, lines 14, 15, page 4, Formula (I); page 4, line 28, page 6, lines 31-34).

The documents D2, D3 and D5-D7 disclose various insecticidal derivatives of pyrazoline (see **D2**: page 3, lines 5-16; page 3, Formula 3 page 3, lines 30, 31; page 4, lines 4, 7; page 26, Table 1; **D7**: page 1, lines 11-13; pages 81-83; pages 90-95).

Lastly, the document D4 discloses the use of 1,5-diphenyl-2-pyrazoline-3-carboxanilide as starting material for the preparation of 1,5-diphenyl-2,3-pyrrolidinedione.

Although some of the compounds disclosed in the above-mentioned documents fall under the formula I of present claim 1, they are nevertheless excluded from the claimed subject-matter by means of a disclaimer.

Consequently, for formal reasons, the presence of novelty has to be acknowledged for the subject-matter of the independent claims 1, 10, 11 and 29-35 and the dependent claims 2-9 and 12-28.

### Inventive step

For the novel subject-matter the document D1 is regarded the closest prior art, since it

likewise addresses compounds being suitable for the treatment of cancer.

For the *first invention*, the distinguishing feature between the novel subject-matter and D1 is the presence of a cyclic substituent instead of the -NH<sub>2</sub> group; for the *second invention* it is the fact that, at the nitrogen atom, there must not be present 2 hydrogen atoms at the same time (see related disclaimer in claim 1).

In the absence of any evidence for an unexpected technical effect linked to these features, the objective problem underlying the novel subject-matter can merely be seen as the provision of further compounds being suitable for the treatment of cancer.

The claimed solution to this very general problem was the modification of the 3-aminocarbonyl derivatives of D1 by replacing the amino group either with a cyclic group (*first invention*) or with an amino group other than NH<sub>2</sub> (*second invention*).

Since the first solution was not derivable from any of the documents on file, either read alone or in combination, for the novel subject-matter underlying the *first invention* the presence of inventive step has to be acknowledged, even in the absence of an *unexpected* technical effect.

It is already known from D1 that aminocarbonyl derivatives of pyrazoline are suitable for the treatment of cancer.

Since the Applicants have failed to provide evidence that the novel subject-matter underlying the *second invention* gives rise to an unexpected technical effect when compared to the solution provided by D1, the International Examining Authority fails to acknowledge the presence of inventive step for the said novel subject-matter.

### **Industrial applicability**

There is no doubt that the subject-matter of the present claims 1-35 is industrially applicable.

### **Re Item VIII**

#### **Certain observations on the international application**

The following phrases lack clarity: "optionally ... substituted" (claims 1, 11); combination of

"optionally" and "preferably" (claim 35).

The present set of claims contains 6 independent use claims (claims 29-34). Bearing in mind that an independent claim must comprise all essential features, it appears consequently that this is not the case with the present 6 claims of the same category. An independent claim, however, which does not comprise all essential features, is not in line with Arts. 5 and 6 PCT.

The breadth of a claim should be such that it could be expected that all possibilities comprised would actually solve the problem underlying the application. Consequently, a claim should only include such possibilities (and their reasonable generalisations) which have been made credible in the specification. It appears thus that the terms "aryl" and "heteroaryl" (claims 1, 11) go far beyond what has actually been verified in the worked Examples on file. Moreover, a person skilled in the art cannot assume that all those possibilities which are presently comprised would be suitable in the sense of solving the present problem.

Apart from this, it appears that the subject-matter of claims 1 and 11 generally lacks support by the description, since the worked Examples on file solely refer to compounds wherein  $R^3$  has the meaning  $-NR^4R^5$ .

This leads the reader automatically to the assumption that the invention does not work with compounds wherein  $R^3$  has a meaning other than  $-NR^4R^5$ .

Any possibly novelty-destroying subject-matter should have been referred to in the description (see disclaimer in claim 1). This had also been in line with Rule 5.1(a)(ii) PCT.